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(54) Title: METHODS FOR THE PURIFICATION OF LEVOFLOXACIN

(57) Abstract: Levofloxacin has been purified by dissolving levofloxacin in a polar solvent at an elevated temperature and crystallizing purified levofloxacin. Preferably, an antioxidant is added to increase the purity.

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## METHODS FOR THE PURIFICATION OF LEVOFLOXACIN

### CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application is a continuation-in-part application of patent application serial number 10/262,965, filed October 3, 2002, which claims the priority of provisional application serial numbers 60/326,958, filed October 3, 2001, 60/334,316, filed November 29, 2001 and 60/354,939, filed February 11, 2002, and patent application serial no. 10/263,192, filed October 3, 2002. The entire content of each of these applications is incorporated herein by reference.

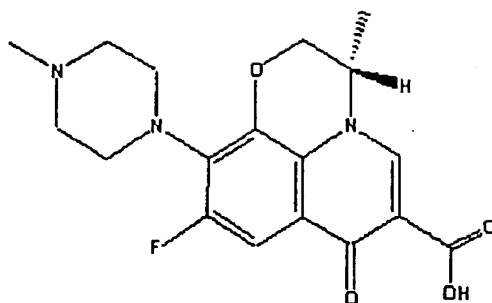
### FIELD OF THE INVENTION

[002] The present invention relates to methods for purifying levofloxacin. In a preferred embodiment, the levofloxacin is prepared with antioxidants.

### BACKGROUND OF THE INVENTION

[003] Levofloxacin is a broad spectrum synthetic antibiotic. Levofloxacin is the S-enantiomer of the racemate, ofloxacin, a fluoroquinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the S-enantiomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves the inhibition of DNA gyrase (bacterial topoisomerase II), an enzyme required for DNA replication, transcription repair and recombination. Levofloxacin is available as LEVAQUIN® which may be orally administered or administered intravenously.

[004] Levofloxacin is a chiral fluorinated carboxyquinolone. Its chemical name is (S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate (CAS Registry No. 100986-85-4). The chemical structure of levofloxacin is shown as Formula I.



Formula I

- [005] U.S. Patent No. 4,382,892 is directed toward pyrido[1,2,3-de][1,4]benzoxazine derivatives and methods of preparing them.
- [006] U.S. Patent No. 5,053,407 is directed toward optically active pyridobenzoxazine derivatives, processes for preparing the same, and intermediates useful for preparing such derivatives.
- [007] U.S. Patent No. 5,051,505 is directed toward processes for preparing piperazinyl quinolone derivatives. The process comprises reacting dihaloquinolones with piperazine derivatives and tetraalkyl ammonium halides in the presence of a polar solvent such as acetonitrile, dimethylformamide, pyridine, sulfolane and dimethyl sulfoxide.
- [008] U.S. Patent No. 5,155,223 is directed toward the preparation of quinolinecarboxylic acids.
- [009] U.S. Patent No. 5,545,737 discloses selectively producing a levofloxacin hemihydrate or monohydrate by controlling the water content of an aqueous solvent in which levofloxacin is dissolved during a crystallization. Arutla et al., *Arzneimittelforschung* (October 1998) 48(10):1024-7, asserts that the racemic mixture ofloxacin has an antioxidant property.
- One disadvantage of the prior art methods for purifying levofloxacin is that they often produce an unsatisfactory yield. For example, 45-65% yields are typical. There remains a need for novel methods for purifying levofloxacin, particularly purified preparations having diminished impurities, such as anti-levofloxacin, desmethyl levofloxacin, N-oxide levofloxacin, desfluoro-levofloxacin and/or decarboxy-levofloxacin.

### SUMMARY OF THE INVENTION

[010] The present invention provides novel processes for purifying levofloxacin. Levofloxacin is dissolved in a polar solvent, preferably one selected from the group consisting of ethyl acetate, ethyl ketone, acetonitrile, an alcohol (preferably butanol), and ketone solvents and aqueous mixtures thereof, at an elevated temperature and crystallized. In one embodiment, the solvent is anhydrous. In another embodiment, a flocculant is added, resulting in a more pure levofloxacin product.

### DETAILED DESCRIPTION OF THE INVENTION

[011] The present invention provides preparations of levofloxacin can be prepared by methods known in the art. levofloxacin crude can be prepared, for example, by the following process. A reactor equipped with a mechanical stirrer, a condenser and a thermometer is charged 87.5g (0.31 mole) of (S)-(-)-9,10-difluoro-3-methyl-7-oxo-8-oxa-5-azabicyclo[4.1.0]hept-2-ene-6-carboxylic acid, 61.3ml (0.62 mole) of N-methylpiperazine. The slurry is stirred at a rate of 100 rpm under nitrogen atmosphere at 80°C until completion of the reaction (monitored by TLC). The slurry is cooled to 75°C and a mixture of isopropanol (675 ml) and water (25 ml) is added dropwise at this temperature over 2 hours. The slurry is stirred for 4 hours, maintained at this temperature for 2 hours and filtered. The solid is then washed with 175 ml of isopropanol and dried under vacuum to obtain levofloxacin crude.

[012] In one embodiment of the present invention, crude levofloxacin is purified. As used herein, "crude levofloxacin" is a relative term meaning more pure. As used herein, "crude levofloxacin" is levofloxacin that has not undergone a purifying crystallization. The preparation of levofloxacin is mixed with a suitable solvent to form a mixture, preferably a suspension. The temperature of the mixture is then elevated to a temperature of the levofloxacin in the solvent. Typically, the elevated temperature is from 50 °C to about 110 °C. Preferably, the mixture is refluxed. Preferably, the levofloxacin is dissolved in the solvent, the mixture is filtrated while hot. The levofloxacin is then precipitated, preferably by slow cooling, and preferably recovered. Levofloxacin preferably has a purity of about 99% or greater.

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preferably about 99.5% or greater.

[013] Polar solvents are generally suitable. Preferably, the solvent is DMSO, methyl ethyl ketone, butanol, acetonitrile, mixtures thereof, or aqueous mixtures thereof. As used herein, the term "polar solvent" is intended as a relative term to mean relatively more polar than another solvent.

[014] The solvent may be anhydrous or may contain a small amount of water. The solvent preferably contains water when a water-soluble antioxidant, such as sodium metabisulfite, is used. The amount of water should be less than about 20% (v/v) and preferably about 10% (v/v) or less. Greater amounts of water tends to decrease the yield. n-BuOH:H<sub>2</sub>O (9:1) and acetonitrile:H<sub>2</sub>O (99:1) are examples of suitable water-containing solvents. Acetonitrile and acetonitrile:H<sub>2</sub>O (99:1) are the most preferred solvents for purifying levofloxacin.

[015] In another embodiment, an antioxidant is added to the mixture prior to precipitation. The antioxidant may be any that prevents the formation of N-oxide levofloxacin, particularly during crystallization. Examples include ascorbic acid, sodium ascorbate, calcium ascorbate, ascorbic palmitate, butylated hydroxyanisole, butylated hydroxytoluene, 2,4,5-trihydroxybutyrophenone, 4-hydroxymethyl-2,6-di-tert-butylphenol, erythorbic acid, gum guaiac, propyl gallate, thioldipropionic acid, dilauryl thioldipropionate, tert-butylhydroquinone, tocopherols (such as vitamin E), and pharmaceutically acceptable salts and mixtures thereof. Preferably, the antioxidant includes sodium metabisulfite or ascorbic acid.

[016] An antioxidant, if used, can be added at various points in the purification process. For example, in one embodiment, an antioxidant is admixed with levofloxacin before or during the crystallization step or before the dissolution step. In another embodiment, an antioxidant is admixed with (S)-(-)-9,10-Difluoro-3-Methyl-7-oxo-2,3-Dihydro-7H-Pyrido[1,2,3-de][1,4]Benzoxazine-6-Carboxylic Acid, a levofloxacin precursor, prior to its conversion to levofloxacin at an elevated temperature.

[017] The amount of antioxidant, when present, is preferably about 0.2% to about 5% by weight, more preferably about 0.2% to about 1 %.

[018] The function and advantages of these and other embodiments of the present invention will be more fully understood from the examples below. The following

examples are intended to illustrate the benefits of the present invention, but do not exemplify the full scope of the invention.

### EXAMPLES

[019] The following Table 1 summarizes the results of the experiments described in the Examples below. The percentage of each component in Table 1 was determined by HPLC using a method based on the European Pharmacopea method for related substances in Ofloxacin.

Table 1: Purification During Crystallization

Ex.	Solvent System	Impurity Profile							
		Crude				Purified			
		Levo	Imp. D Anti	Imp. E DesMe	Imp. F N-Oxide	Levo	Imp. D Anti	Imp. E DesMe	Imp. F N-Oxide
1	n-Bu-OH	99.44	ND	0.11	0.19	99.60	ND	0.09	0.19
2	n-BuOH Asc. acid (2.4%)	99.58	ND	0.11	0.21	99.78	ND	0.08	ND
3	n-BuOH/H <sub>2</sub> O Na <sub>2</sub> S <sub>2</sub> O <sub>5</sub> (0.6%)	99.58	ND	0.11	0.21	99.85	ND	0.08	ND
4	ACN	99.44	ND	0.11	0.19	99.67	ND	0.04	0.15
5	ACN:H <sub>2</sub> O	99.64	0.08	0.09	<0.03	99.85	ND	0.06	<0.03
6	ACN:H <sub>2</sub> O Na <sub>2</sub> S <sub>2</sub> O <sub>5</sub> (0.2%)	99.77	<0.03	0.05	<0.03	99.93	ND	<0.03	ND
7	ACN Na <sub>2</sub> S <sub>2</sub> O <sub>5</sub> (0.5%)	99.58	ND	0.11	0.21	99.70	ND	0.06	0.1
8	DMSO:H <sub>2</sub> O	99.44	ND	0.11	0.19	99.75	ND	0.06	0.13
9	MEK	99.44	ND	0.11	0.19	99.58	ND	ND	0.26
10	ACN:H <sub>2</sub> O (90:10) Na <sub>2</sub> S <sub>2</sub> O <sub>5</sub> (0.5%)	99.58	ND	0.11	0.21	99.69	ND	0.08	ND

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11	ACN:H <sub>2</sub> O (95:5) Na <sub>2</sub> S <sub>2</sub> O <sub>5</sub> (0.5%)	99.58	ND	0.11	0.21	99.74	ND	0.06	ND
12	ACN:H <sub>2</sub> O (95:5) Na <sub>2</sub> S <sub>2</sub> O <sub>5</sub> (0.25%)	99.58	ND	0.11	0.21	99.81	ND	0.08	ND
13	DMSO Asc. Acid (0.6%)	99.80	ND	0.03	0.02	--	--	--	--
14	DMSO Na <sub>2</sub> S <sub>2</sub> O <sub>5</sub> (0.5 eq.)	99.77	0.04	0.10	<0.03	--	--	--	--

ND = Not detected.

#### **Example 1: n-BuOH**

[020] 1g of levofloxacin crude was put in suspension in 7 ml of n-BuOH. The mixture was heated to reflux temperature until complete dissolution of the material. Then the solution was cooled to RT over a period of 2.5 hours. The precipitate was filtrated under vacuum, washed with n-BuOH and dried at 60°C in a vacuum oven to give 810 mg (81%) of purified levofloxacin hemihydrate.

#### **Example 2: n-BuOH / Ascorbic acid**

[021] 1.5 g of levofloxacin crude and 36 mg of ascorbic acid were put in suspension in 9.5 ml of n-BuOH under inert atmosphere. The mixture was heated to reflux temperature and a hot filtration was performed. The solution was then evaporated to dryness and n-BuOH (10 ml) was added. The mixture was heated to reflux until complete dissolution and then cooled to RT over a period of 1.5 hour. The precipitate was filtrated under vacuum, washed with n-BuOH (4 ml) and dried at 60°C in a vacuum oven to give 840 mg (56%) of purified levofloxacin hemihydrate.

#### **Example 3: n-BuOH:H<sub>2</sub>O (9:1) / Metabisulfite**

[022] 1.5 g of levofloxacin crude and 10 mg of sodium metabisulfite were put in suspension in 6 ml of a mixture n-BuOH:H<sub>2</sub>O (9:1) under nitrogen atmosphere. The mixture was heated to reflux temperature until complete dissolution of the material. Then

the solution was cooled to RT over a period of 1.5 hours. The precipitate was filtrated under vacuum, washed with a mixture n-BuOH:H<sub>2</sub>O (9:1) (4 ml) and dried at 60°C in a vacuum oven to give 1.2 g (81%) of purified levofloxacin hemihydrate. The purified levofloxacin hemihydrate contained virtually no N-oxide levofloxacin.

**Example 4: ACN**

[023] 1.5g of levofloxacin crude was put in suspension in 10.5 ml of ACN. The mixture was heated to reflux temperature until complete dissolution of the material. Then the solution was cooled to 0°C over a period of 20 minutes. The precipitate was filtrated under vacuum, washed with ACN (1.5 ml) and dried at 30°C in a vacuum oven to give 1.15 g (77%) of purified levofloxacin (hemihydrate/monohydrate mixture). The purified levofloxacin contained approximately half the amount of desmethyl levofloxacin as that in the crude sample.

**Example 5: ACN: H<sub>2</sub>O (99:1)**

[024] 25 g of wet levofloxacin crude (about 22.17g or dry levofloxacin) was put in suspension in 225 mL of mixture ACN:H<sub>2</sub>O (99:1) under nitrogen atmosphere. The mixture was heated to reflux during 1 hour and then filtrated under vacuum with Hyflow when still hot. Then the solution was heated again to reflux and cooled to 0°C over a period of 1 hour. The precipitate was filtrated under vacuum, washed with ACN:H<sub>2</sub>O(2x12 mL) and dried in a vacuum oven to give 18.6 g (84%) of purified levofloxacin hemihydrate. The purified levofloxacin hemihydrate contained approximately one-third less desmethyl levofloxacin than in the crude sample.

**Example 6: ACN:H<sub>2</sub>O (99:1) / Metabisulfite**

[025] 8 g of wet levofloxacin crude (about 5.6g of dry levofloxacin) and 14 mg of sodium metabisulfite were put in suspension in 39 ml of a mixture ACN:H<sub>2</sub>O (99:1) under nitrogen atmosphere. The mixture was heated to reflux during 1 hour, 0.65 g of Hyflo was added and the reflux was continued for an additional half an hour. The mixture was filtrated under vacuum when still hot. Then the solution was cooled to 3°C over a period of 30 minutes. The precipitate was filtrated under vacuum, washed with a mixture ACN:H<sub>2</sub>O (99:1) (5 ml) and dried at 60°C in a vacuum oven to give 1.77 g (31%) of purified levofloxacin. Technical problems during the hot filtration decreased the yield.



**Example 7: ACN / Metabisulfate**

[026] 1.5 g of levofloxacin crude and 8 mg of sodium metabisulfite were put in suspension in 10.5 ml of ACN under nitrogen atmosphere. The mixture was heated to reflux temperature and a hot filtration was performed. Then the solution was heated again to reflux temperature until complete dissolution of the material. The solution was then cooled to 0°C over a period of 30 minutes. The precipitate was filtrated under vacuum and dried at 60°C in a vacuum oven to give 1.04 g (69%) of purified levofloxacin. The purified levofloxacin contained approximately half the amount of N-oxide levofloxacin as that in the crude sample.

**Example 8: DMSO/H<sub>2</sub>O**

[027] 1g of levofloxacin crude was put in suspension in 1.5 ml of DMSO. The mixture was heated to 108°C until complete dissolution of the material. Then H<sub>2</sub>O (7.5 ml) was added over 10 minutes and the mixture was cooled to RT. The precipitate was filtrated under vacuum, washed with 1 ml of a mixture DMSO:H<sub>2</sub>O 1:5 and dried at 60°C in an air-flow oven to give 840 mg (84%) of purified levofloxacin hemihydrate.

**Example 9: MEK**

[028] 1.5g of levofloxacin crude was put in suspension in 15 ml of MEK. The mixture was heated to reflux temperature until complete dissolution of the material. Then the solution was cooled to -5°C over a period of 3 hours. The precipitate was filtrated under vacuum, washed with 1.5 ml of MEK and dried at 30°C in a vacuum oven to give 840 mg (84%) of purified levofloxacin hemihydrate.

**Example 10: ACN:H<sub>2</sub>O (9:1) / Metabisulfite**

[029] 1.5 g of levofloxacin crude and 8 mg of sodium metabisulfite were put in suspension in 10.5 ml of a mixture ACN:H<sub>2</sub>O 9:1 under nitrogen atmosphere. The mixture was heated to reflux temperature until complete dissolution of the material. Then the solution was cooled to RT over a period of 30 minutes. The precipitate was filtrated under vacuum, washed with a mixture ACN:H<sub>2</sub>O 9:1 (4 ml) and dried at 60°C in a vacuum oven to give 1.16 g (77%) of pure levofloxacin.

**Example 11: ACN:H<sub>2</sub>O (95:5) / Metabisulfite (8 mg)**

[030] 1.5 g of levofloxacin crude and 8 mg of sodium metabisulfite were put in suspension in 10.5 ml of a mixture ACN:H<sub>2</sub>O 95:5 under nitrogen atmosphere. The

mixture was heated to reflux temperature and a hot filtration was performed. The solution was heated again to reflux temperature then cooled to 3°C in 30 minutes. The precipitate was filtrated under vacuum and dried at 60°C in a vacuum oven to give 500 mg (33%) of pure levofloxacin.

**Example 12: ACN:H<sub>2</sub>O (95:5) / Metabisulfite (4 mg)**

[031] 1.5 g of levofloxacin crude and 4 mg of sodium metabisulfite were put in suspension in 15 ml of a mixture ACN:H<sub>2</sub>O 95:5 under nitrogen atmosphere. The mixture was heated to reflux temperature until complete dissolution of the material. Then the solution was cooled to 3°C over a period of 2 hours. The precipitate was filtrated under vacuum and dried at 60°C in a vacuum oven to give 1.3 g (86.7%) of pure Levofloxacin.

**Example 13: DMSO / Ascorbic Acid**

[032] In a three necks flask equipped of a condenser were put in suspension in 3.5 ml of DMSO at 80°C under nitrogen atmosphere 5g (17.8 mmol) of (S)-(-)-9,10-Difluoro-3-Methyl-7-oxo-2,3-Dihydro-7H-Pyrido[1,2,3-de][1,4]Benzoxazine-6-Carboxylic Acid, 4.46g (44.6 mmol), 31 mg (0.17 mmol) of ascorbic acid. The reaction mixture was heated at this temperature (4h30) until completion of the reaction. Then the solution was cooled to 70°C and IPA (40 ml) was added dropwise. The mixture was cooled to 0°C in 1 hour and then stirred at this temperature for 30 minutes. The precipitate was filtrated under vacuum, washed with IPA (10ml) and dried at 60°C in a vacuum oven to give 5.63 g (87.6%) of pure levofloxacin.

**Example 14: DMSO / Metabisulfite**

[033] In a three necks flask equipped of a condenser were put in suspension in 7 ml of DMSO at 80°C under nitrogen atmosphere 10 g (35.5 mmol) of (S)-(-)-9,10-Difluoro-3-Methyl-7-oxo-2,3-Dihydro-7H-Pyrido[1,2,3-de][1,4]Benzoxazine-6-Carboxylic Acid, 9.0g (90 mmol), 34 mg (0.17 mmol) of sodium metabisulfite. The reaction mixture was heated at this temperature (5h30) until completion of the reaction. Then the solution was cooled to 70°C and IPA (40 ml) was added dropwise. The mixture was cooled to 0°C in 1 hour and then stirred at this temperature for 30 minutes. The precipitate was filtrated under vacuum, washed with IPA (10ml) and dried at 60°C in a vacuum oven to give 11.8 g (92.4%) of pure levofloxacin.

**What is claimed is:**

1. A process for preparing levofloxacin having a purity of about 99% or greater, comprising:  
dissolving levofloxacin in a polar solvent at an elevated temperature; and  
crystallizing purified levofloxacin.
2. The process of claim 1, wherein the purity of the purified levofloxacin is about 99.5% by weight or greater.
3. The process of claim 1, wherein the elevated temperature ranges from about 80 °C to about 110 °C.
4. The process of claim 1, wherein the elevated temperature is the reflux temperature of the solution.
5. The process of claim 1, wherein the polar solvent is selected from the group consisting of dimethyl sulfoxide, methyl ethyl ketone, acetonitrile, butanol, mixtures thereof, and aqueous mixtures thereof.
6. The process of claim 1, wherein the solvent is acetonitrile.
7. The process of claim 1, wherein the solvent is a mixture of acetonitrile and water, wherein the amount of water in the solvent is about 10% or less.
8. The process of claim 1, wherein the amount of desmethyl levofloxacin in the purified levofloxacin is at least one-third less than the amount in the initial levofloxacin.
9. The process of claim 1, further comprising adding an antioxidant prior to the crystallizing step.
10. The process of claim 9, wherein the antioxidant is selected from the group consisting of ascorbic acid, sodium ascorbate, calcium ascorbate, ascorbic palmitate, butylated hydroxyanisole, butylated hydroxytoluene, 2,4,5-trihydroxybutyrophenone, 4-hydroxymethyl-2,6-di-tert-butylphenol, erythorbic acid, gum guaiac, propyl gallate, thiodipropionic acid, dilauryl thiodipropionate, tert-butylhydroquinone, tocopherols, and pharmaceutically acceptable salts and mixtures thereof.
11. The process of claim 9, wherein the antioxidant is sodium metabisulfite.
12. The process of claim 9, wherein the antioxidant is ascorbic acid.
13. The process of claim 9, wherein the amount of N-oxide levofloxacin in the purified levofloxacin is at least one-third less than the amount in the initial levofloxacin.

14. The process of claim 9, wherein the amount of N-oxide levofloxacin in the purified levofloxacin is about 0.1% or less.
15. The process of claim 9, wherein the purity of the purified levofloxacin is about 99.5% by weight or greater.
16. The process of claim 9, further comprising a step of determining whether the initial levofloxacin contains an amount of N-oxide levofloxacin that is detectable by HPLC.
17. The process of claim 9, wherein the solvent is acetonitrile and wherein the purified levofloxacin is substantially pure levofloxacin hemihydrate.
18. The process of claim 1, and wherein the purified levofloxacin is substantially pure levofloxacin hemihydrate.
19. A process for preparing levofloxacin hemihydrate having a purity of about 99% or greater, comprising:
  - dissolving levofloxacin in a polar solvent at an elevated temperature; and
  - crystallizing levofloxacin hemihydrate.
20. The process of claim 19, wherein the elevated temperature ranges from about 80 °C to about 110 °C.
21. The process of claim 19, wherein the elevated temperature is the reflux temperature of the solution.
22. The process of claim 19, wherein the solvent is selected from the group consisting of acetonitrile, dimethyl sulfoxide:H<sub>2</sub>O, methyl ethyl ketone, butanol, and mixtures thereof.
23. The process of claim 19, wherein the solvent is dimethyl sulfoxide:H<sub>2</sub>O in a ratio of about 1:5.
24. The process of claim 19, wherein the solvent is methyl ethyl ketone.
25. The process of claim 19, wherein the solvent is n-butanol.
26. The process of claim 19, wherein the solvent is acetonitrile.
27. The product of the process of claim 1.
28. The product of the process of claim 9.
29. The product of the process of claim 19.
30. A process for preparing levofloxacin having a purity of about 99% or greater, comprising:

dissolving levofloxacin in a polar solvent;  
adding an antioxidant; and  
crystallizing purified levofloxacin,

wherein the adding step occurs before or after the dissolving step and before the crystallizing step.

31. The process of claim 9, wherein the antioxidant ranges from about 0.2% to about 5% by weight levofloxacin.
32. The process of claim 9, wherein the antioxidant is added to the levofloxacin before the dissolving step.
33. The process of claim 1, further comprising adding an antioxidant during the crystallization step.
34. A process for preparing levofloxacin having a purity of about 99% or greater comprising converting (S)-(-)-9,10-Difluoro-3-Methyl-7-oxo-2,3-Dihydro-7H-Pyrido[1,2,3-de][1,4]Benzoxazine-6-Carboxylic Acid to levofloxacin at an elevated temperature in the presence of an antioxidant.
35. The process of claim 34, wherein the purity of the levofloxacin is about 99.5% by weight or greater.
36. The process of claim 34, wherein the amount of N-oxide levofloxacin in the levofloxacin is about 0.1% or less.